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EDITORIAL

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The clinical evaluation of penicillin allergy: what is necessary, sufficient and safe given the materials currently available?

This editorial discusses the findings of the paper in this issue by M. J. Torres et al. [4], pp. 1595–1601.

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Adverse drug reactions, commonly called drug 'allergies' in the medical record, are a large and growing problem. Women report more drug 'allergies' than men. The prevalence of drug 'allergy' increases with increasing age. There is a baseline incidence of new 'allergy' reports with all antibiotic use that varies significantly by gender and antibiotic class [1]. The rate of adverse reactions may be higher when antibiotics are used inappropriately in the setting of certain viral infections [2].

Penicillin 'allergy' is still the most common drug 'allergy' in Europe and North America, with about 10% prevalence. Amoxicillin is the most common penicillin class antibiotic used in North America and Europe. Almost all individuals with a penicillin 'allergy' never have the diagnosis verified and carry it for the rest of their lives. The high prevalence of penicillin 'allergy' contributes to suboptimal antibiotic use, more antibiotic resistance and increased health care expenditures.

Most reported penicillin 'allergy' is not associated with clinically significant IgE directed against penicillin, the amoxicillin specific side chain or penicillin metabolites. Only a small minority of individuals with a history of penicillin 'allergy' have reproducible T cell mediated reactions to penicillin or amoxicillin. Oral challenges with penicillin in properly selected subjects with expert supervision are safe, even if an IgE-mediated event is suspected [2]. Food and non-steroidal anti-inflammatory drug challenges, which are also potentially life-threatening, are routinely done in Allergists' offices.

There have been a number of confusing and contradictory papers in the world's literature on the diagnosis of penicillin allergy. There have been trans-Atlantic disagreements on the relative significance of isolated amoxicillin allergy, the appropriate concentration of amoxicillin to use and even the size of a clinically significant positive skin test result. Clinicians are often paralysed by increasingly complex published practice guidelines [3]. The net result is that very few individuals with a penicillin class antibiotic 'allergy' ever have the diagnosis verified. Torres and co-workers, in this issue of the Journal, describe a new preparation of amoxicillin to replace the intravenous amoxicillin they used previously as a skin test and *in vitro* reagent [4].

In most recent large studies over the past decade, on both sides of the Atlantic, involving average patients with a history of penicillin 'allergy', <5% are penicillin skin test-positive, excluding testing with high dose amoxicillin [5–7]. There are anecdotal reports that penicillin skin testing, as commonly performed, is too sensitive, with less than half of penicillin skin test-positive individuals receiving oral penicillin having any reaction [2, 8]. Oral challenges have not been widely adopted as a primary test modality, mainly out of fear of causing an anaphylactic reaction. Acute anaphylaxis with oral penicillin use is extremely rare. An acute onset, within 1 h of challenge, urticarial or anaphylactic reaction, is currently considered the 'gold standard test' to verify clinically significant IgE-mediated penicillin allergy.

A commercial version of the major determinant, penicilloyl-poly-lysine (Pre-Pen®; ALK-Abello, Round Rock, TX, USA), has been sold in the USA since 1974, with intermittent unavailability over the last decade. Since its reintroduction in 2010, there have only been

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15 000 doses of Pre-Pen® sold. Pre-Pen® is not currently available in Europe or Canada. A maximum of 40 000 doses of Pre-Pen® had ever been sold per year in the USA. There are currently about 30 million Americans with a history of penicillin allergy. In Europe, Diater Laboratorios, S.A., Madrid, Spain, sells a kit that contains penicilloyl-poly-lysine and a minor determinant mixture.

A positive immediate-type hypersensitivity skin test or blood allergy test, such as an enzyme-linked immunoassay for IgE or antigen-specific basophil activation, to an antibiotic does not define clinically significant IgE-mediated allergy. It is necessary to have reproducible IgE-mediated symptoms with re-exposure. This holds for IgE-mediated allergy to foods, venoms, pollens and antibiotics. Using penicillin allergy tests that have high rates of false positives, allergists can make the problem worse. If the criterion for a positive immediate-type hypersensitivity anti-penicillin skin test is set too low, for example, 3 mm of weal instead of 5 mm of weal, then many more women will have false positive skin test results [9, 10]. There has been a gradual trend towards calling a smaller and smaller penicillin skin test result positive. In a seminal paper from 1992 looking at major and minor penicillin derivatives in hospitalized adults, a 1+ reaction was 4–6 mm weal with flare greater than weal, 2+ was 7–9 mm, 3+ was 10–12 mm and 4+ was greater than 13 mm [11]. The FDA approved package insert for Pre-Pen®, and notes that a positive test result is 5–15 mm or greater. Many investigators now unfortunately use 3 or 4 mm of weal as the criteria for a positive test result [9, 12]. *In vitro* tests, specifically the commercially available fluorescent enzyme immunoassay for anti-penicillin and anti-amoxicillin IgE, are not useful in diagnosing clinically significant penicillin allergy, because they do not correlate to challenge reactions [2, 10].

There has been significant disagreement between European and North American clinicians regarding the concentration of amoxicillin that should be used for skin testing, but interestingly not the concentration of penicillin, penicilloate or penilloate. Even cephalosporins are typically used at about 2 mg/mL or 0.005 M for immediate-type hypersensitivity skin testing by both European and North American clinicians. If amoxicillin is used at 20–25 mg/mL, 0.5–0.6 M and 0.02 mL is used for an intradermal test, as is commonly done in Europe, there is potential systemic exposure to 0.4–0.5 mg of amoxicillin. This is more than the third dose recommended by the Centers for Disease Control and Prevention during an oral penicillin desensitization protocol, and may cause systemic symptoms in highly sensitive individuals [13].

There is a good consensus that IgE-mediated penicillin allergy can be diagnosed using the major determinant, penicilloyl-poly-lysine and one or more minor determinants, most importantly native penicillin, but also including penicilloate, penilloate and amoxicillin. Some individuals produce IgE that binds to the unique side chain of amoxicillin, but not to any of the core penicillin epitopes. The clinical significance of this amoxicillin specific IgE is in question. There is a developing consensus that oral challenges should be part of the penicillin allergy work-up to identify false negative skin tests and clinically significant T cell mediated reactions.

The gold standard for evaluating penicillin allergy testing and challenge protocols should be the clinical outcomes that occur with future therapeutic penicillin class antibiotic exposure. A new 'allergy' is reported after 0.5–4% of all therapeutic antibiotic use, depending on the specific antibiotic class and patient gender [1]. This is commonly ignored when calculating the positive and negative predictive value of penicillin skin test and challenge protocols. The advent of completely electronic medical records at a very large healthcare organization in the USA, Kaiser Permanente, has made it possible to follow, long-term, the adverse reactions associated with all therapeutic antibiotic use after penicillin skin testing in large populations [14].

Toxic epidermal necrolysis, Stevens Johnson syndrome, severe hepatitis, drug reaction with eosinophilia and systemic symptoms syndrome, interstitial nephritis and haemolytic anaemia are not mediated through IgE. Testing, challenging or attempting desensitization in individuals with a history of these conditions associated with use of a penicillin class antibiotic is not recommended.

Since the reintroduction of commercial Pre-Pen® in the USA in June 2010, we have used it along with native penicillin G and amoxicillin, both at 0.01 M, for all of our penicillin skin testing. We are no longer using the minor determinants, penicilloate and penilloate, which we produced in 1994 [15]. We obtain the penicillin G from our pharmacy and dilute it to 0.01 M. We obtain amoxicillin, as the pure acid, from non-medical sources (A8523 – Sigma-Aldrich.com). We dissolve it in buffered saline, adjust the pH to 7.4 and dilute to a final concentration of 0.01 M. We store the unit doses of the filter-sterilized amoxicillin solution at −70°C and thaw only once just prior to use. Puncture testing is completed prior to intradermal testing, and a positive test result is a weal 5 mm or larger at 15 min, with a flare greater than the weal, for both puncture and intradermal testing. All individuals with negative skin test results are given an oral amoxicillin or penicillin challenge, typically 250–500 mg for an adult or an equivalent weight adjusted dose for young children, and observed for 1 h.

We have tested 242 individuals with this protocol between 7 June 2010 and 22 June 2011. This cohort was 62% women, had a mean age of 40.8 ± 26.7 years

and a mean time since reaction of 19.7 ± 19.5 years, very closely mirroring random patients with a history of penicillin 'allergy'. We have only had two (0.83%, 95% CI: 0.23–2.96) positive skin test results over the past year, both intradermal test-positive to Pre-Pen®. There have been no positive skin test results to either native penicillin G or amoxicillin. There were four (1.65%, 95% CI: 0.64–4.17) acute challenge reactions, all mild hives, starting within 1 h. There have been no episodes of anaphylaxis. There have been no delayed onset rashes within 5 days of the skin test and challenge.

A recent report by Caubet and co-workers is a breakthrough in the evaluation of children with beta-lactam, mainly amoxicillin associated, associated adverse drug reactions [2]. It is the first prospective look at a well-characterized population, captured early during the index reaction and followed with extensive drug allergy and viral testing over a several month period. All patients received oral challenges. Only a minority of penicillin skin test-positive children had oral challenge reactions. Most challenge reactions were delayed onset, which was unexpected for an IgE-mediated event. The reactions were not more severe than the index reactions. Many of the challenge reactions were associated with evidence for recent Epstein Barr virus (EBV) or other viral infection. Having an acute EBV infection 2 months ago may be enough to significantly increase the risk of having a rash associated with amoxicillin use today. This population was selected to exclude individuals with a history of anaphylaxis, but such patients only account for a minority of reactions.

In summary, penicillin allergy evaluations can be safely accomplished with the following steps. Screen out individuals with a history of toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, blistering eruptions, severe hepatitis, serum sickness, nephritis and/or haemolytic anaemia. Individuals with a history of anaphylaxis, shortness of breath, hives, other rashes and other conditions not excluded above may undergo penicillin skin testing. If the penicillin skin tests are negative, all should have oral challenges. Children with a history of urticaria or macular papular rashes may go directly to oral challenge.

Future penicillin allergy evaluation protocols need to follow tested and challenged individuals for several years to determine the incidence of new adverse reactions associated with beta-lactam and other therapeutic antibiotic use. The goal should be to find the simplest, safe and effective work-up that uses materials that are commercially available around the world. This may only require skin testing with penicilloyl-poly-lysine and native penicillin G, followed by an oral challenge with amoxicillin if negative. It may only require an oral challenge with amoxicillin. Even with a perfect protocol there will be future adverse reactions associated with all antibiotic use. We know there will be a low rate of re-sensitization [16]. Ideally, the vast majority of individuals who carry a history of penicillin 'allergy' can have it removed from their medical record. Allergists and Clinical Immunologists should actively address this large and growing problem and dramatically increase the number of individuals who undergo penicillin skin testing and oral challenges.

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